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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

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EXAMINER

ART UNIT	PAPER NUMBER
	17

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/311,689	RAO ET AL	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,28-47,49,50 and 52-95* is/are pending in the application.

4a) Of the above claim(s) *1-8,33-47,49,50,52,53 and 90-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-25,28-32 and 54-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8,14* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Application Status

1. A preliminary amendment was filed on March 19, 2001, which amended the pending claims. Claims 1-25, 28-47, 49-50, and 52-95 are pending in the instant application.

Election

2. Applicants' election of Group III in Paper No. 12 is acknowledged; this Group is drawn to polypeptides relating to the particular SEQ ID NO:2 and variation thereof (the Claim numbers may have changed due to Applicants' amendments). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-25, 28-47, 49-50, and 52-95 are pending in the instant application. Claims 1-8, 33-47, 49-50, 52-53, and 90-95 are withdrawn from consideration. Thus, Claims 9-25, 28-32, and 54-89 will be examined herein.

Priority

3. The instant application is granted the benefit of priority of U.S. Application 08/740,682, filed on November 1, 1996. The instant application is also granted the benefit of priority of U.S. Application and 09/297,418, filed on April 30, 1999, which claims priority to PCT/US97/20441 filed on October 31, 1997.

Information Disclosure Statement

4. The information disclosure statements filed on July 19, 1999 (Paper No. 14), September 20, 1999 (Paper No. 5), and January 16, 2001 (Paper No. 8) have been reviewed, and their references have been considered as shown by the Examiner's initials on the attached copies.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Compliance with the Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

(a) In Figures 1 and 2, amino acid sequences are disclosed without benefit of SEQ ID NOs.

(b) On pages 50-54, numerous DNA sequences are disclosed without benefit of SEQ ID NOs.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the

same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

7. The specification is objected to for inappropriate notation of an internet address. On page 12, line 17, an internet address is cited in an unacceptable form. See M.P.E.P. 707.05(e) for the acceptable notation of an internet address.

8. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter. It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the protein and its source(s). for completeness.

9. The amendments filed on January 16, 2001 (Amdt A) and March 19, 2001 (Amdt B) are objected to under 35 U.S.C. 132 because they introduce new matter into the disclosure, particularly into the claims. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

a) In Claims 9 and 54, "8-15 mole % methionine".

b) In Claims 9 and 55, "13-25 mole % threonine".

c) In Claim 9, "6-12 mole % tryptophan".

d) In Claim 9, "12-20 mole % isoleucine".

e) In Claim 59, "at least 60% sequence identity...SEQ ID NO:2" and "about 15% or more lysine".

f) In Claim 60, "about 20 mole % or more lysine".

g) In Claim 61, "at 4 to about 34 positions" and "Sequence ID No. 2 positions 19-53 and 63-83".

h) In Claim 72, "at least 4 to about 34...amino acids" and "Sequence ID No. 2 positions 19-83".

i) In Claim 74, "at 6 to about 34 positions" and "Sequence ID No. 2 positions 19-53 and 63-83".

j) In Claim 76, "at least 23 amino acids in length" and "at least 11 non-native essential amino acids" and "Sequence ID No. 2 positions 19-83"

k) In Claim 78, "at least 23 amino acids in length" and "at least 64% identity to ... positions 19-83 in Sequence ID No. 2" and "at least one cysteine residue in ... positions 19-83 in Sequence ID No. 2".

l) In Claim 79, "at least 23 amino acids in length" and "at least 60% identity to ... Sequence ID No. 6" and "at least one cysteine residue in ... positions 19-83 in Sequence ID No. 2".

m) In Claim 80, "at least 74% identity".

n) In Claim 81, "at least 23 amino acids in length" and "at least 57% identity to ... Sequence ID No. 8" and "at least one cysteine residue in ... positions 19-83 in Sequence ID No. 2".

o) In Claim 82, "at least 67% identity".

p) In Claim 83, "at least 23 amino acids in length" and "at least 57% identity to ... Sequence ID No. 10" and "at least one cysteine residue in ... positions 19-83 in Sequence ID No. 2".

q) In Claim 84, "at least 67% identity".

r) In Claim 87, "at least 20 amino acids in length" and "modified to have at least seven non-native essential amino acid residues".

Applicants are required to cancel the new matter in the reply to this Office Action or to point out **precisely** (page and line number) where in the instant application, or where in any incorporated-by-reference publications, clear support for the amendments can be found. Particularly, the Examiner notes that the numbers above from the amended claims must *explicitly* be found as *exact* references for **clear** support (i.e., the numbers and/or ranges must have been considered at the time of filing as the invention). For example, the support cited for "at least 64% identity" in amendment B is that a single embodiment having 64% identity is disclosed; this disclosure possibly supports an embodiment having 64% identity, but in no way supports *at least* 64% identity since *the range* is not described by the single embodiment. This same argument would be set forth for ranges on mole percent and amino acid positions corresponding to SEQ ID NO:2.

Objections to the Claims

10. Claims 54-55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The mole percent limitations in the instant claims are already

recited in the parent Claim 9. See also the 112, second paragraph rejection concerning the confusion about the mole percent combinations.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 9-20 and 54-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The **persistent use of numerals** in the claims, when referring to (a) sequence length, (b) mole percent, (c) positions in defined sequences, (d) number of modifications, and (e) particular modifications, renders the claims very difficult to interpret. The Examiner suggests, using numerals for mole percents (15-35 mole % lysine), positions in defined sequences (positions 1, 8, etc.) and particular modifications (T22C); however, the Examiner recommends amending the claims to use words for sequence length (fifty amino acids in length) and number of modifications (modified to contain seven or more). Such amendments throughout the claims will ease confusion considerably.

12. Claims 9 and 54-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim language of Claim 9 is confusing as to whether the "**composition...or in combinations thereof**" (the term composition which typically encompasses all of what follows) requires that all the listed mole percents be present in a

polypeptide or if only one mole percent is required. The Examiner suggests, if only one mole percent is required, that Claim 9 be amended to include the following phrase ---altered to have a composition selected from the following--- and the Markush group should be joined by ---and--- (not "or" as claimed presently). The instant claims will be given their broadest reasonable interpretation for the examination herein; thus, only a single mole percent will be required to meet the claim limitations. However, Claims 54-55 are objected to for not being further limiting based on a less broad interpretation (see above).

13. Claims 9, 54, 55, 59, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The concept of "**mole %**" is unclear as to whether whole numbers are required. In other words, does 11.8 mole % read on a claim limitation of 12 mole % by virtue of rounding up? The Examiner suggests inserting ---at least 12 mole percent--- to clarify in the instant claims if whole integers are required.

14. Claims 10-18 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 claims not only corresponds to SEQ ID NO:2, but also **truncated versions** of SEQ ID NO:2. However, the positions for modification extend almost the entire length of SEQ ID NO:2. Thus, the extent to which truncated forms fall within the scope of the instant claims is unclear.

15. Claims 10-18, 56, and 61-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "**modified to contain**" is confusing since the sequences claimed contain essential amino acids prior to modification. It is unclear whether an essential amino acid needs to be added by modification to the sequence or if, once modified, the sequences must *still* contain essential amino acids.

16. Claims 10-25, 56, and 61-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 10, 19, 21, 56, 61, 69, 72, 74, 76, 78, 79, 81, 83, 85, and 86, the phrase "**corresponding to**" or "correspond to" is confusing because the relatedness of SEQ ID NO:2 to all other possible polypeptides is not clear. Particularly, how to identify which residues "correspond" is unclear. See also the 112, first paragraph, enablement rejection below.

17. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 limits the essential amino acid particular amino acids and their **conservative substitutions**. The instant specification defines conservative substitutions on page 10, lines 20-30, and defines conservative/essential substitutions on page 10, lines 29-30. The variation between Ile, Leu, Met, and Val is clear and consistent between conservative substitutions and conservative/essential substitutions. In contrast, conservative substitutions between Ala, Ser, **Thr**, and Cys are inconsistent with conservative/essential substitutions

between **Thr** and Lys. Moreover, conservative substitutions between **Lys** and Arg are inconsistent with conservative/essential substitutions between **Lys** and Thr. Thus, the possible substitutions of Lys and Thr that fall within the scope of the claim are unclear.

18. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**reduced**" in claim 12 is a relative term which renders the claim indefinite. The term "reduced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

19. Claims 13, 14, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**protein**" in the instant claims does not have proper **antecedent basis** in the parent claim (10) which refers to polypeptides.

20. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**comprising**" should be recited as **---further comprising---** since the modifications cited are in addition to the positions in the parent claim (10).

21. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is confusing for two reasons: 1) the **further comprising** language

while not all the mutations in the list are options in the parent claim, and 2) the **brackets** around the apparent pairs of mutations.

Firstly, for the pairs of mutations [22,82] and [23,81], which positions are also noted in the parent claim, Claim 14 should be claimed as "comprising" since these are sites of mutation within the limitations of Claim 10 and can be consider within the "7 or more" mutations required in Claim 10. However, for the pair of mutations [53,70], which positions are not noted in the parent claim, Claim 14 should be claimed as "further comprising" since these are *additional* sites of mutation and cannot be consider within the "7 or more" mutations of Claim 10. The Examiner suggests that Claim 14 be divided into two dependent claims to clearly claim the intended subject matter.

Secondly, the brackets around the pairs of mutations, in light of the specification, indicate pairs. However, this limitation is not clear in the instant claim. The Examiner suggests amending the claim language to read

---comprising one of the following pairs of substitutions:

T22C and V82C; or

E23C and R81C---

or to read

---further comprising the pair of substitutions that is V53C and V70C---

22. Claims 15-18 and 65-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are confusing for four reasons: 1) in Claim 15 and Claim 65, the phrase "**amino-terminal extension**" is unclear, 2) in Claim 16, the

phrase "**nutritionally-enhancing polypeptide**" is unclear, 3) in Claim 17 and Claim 66, the **set of limitations** on the amino-terminal extension are all unclear, and 4) in Claim 18, the location of the inclusion of **residues 1 to 18** of SEQ ID NOs: 2 or 12 is confusing.

The phrase "amino-terminal extension" is unclear because the term extending or extension implies using more of the same components, that is polypeptide; however, no such limitation is expressed in the claims or in the specification.

The phrase "nutritionally-enhancing polypeptide" is unclear. The definition in the instant specification is on page 9, lines 1-3, and describes "adding nutritional components" without any definite description as to what those nutritional components are. Any polypeptide can enhance nutrition since its components, amino acids, are the building blocks of other proteins. The term "enhancing" is a relative term and to comparison is described. This phrase only further limits the parent claim by virtue of the inclusion of the term "polypeptide" which, as noted above, is not required by the term "amino-terminal extension" although it is implied.

The terms which limit the amino-terminal extension in Claim 17 are wholly unclear. A "start signal" is used in the art to describe nucleic acids, not proteins; also, in Claim 66, the term "start methionine" is unclear since the term ---methionine--- would seem to be sufficient. In the art, the terms "transit sequence", "transit peptide", and "signal peptide" have the same definition with respect to polypeptides (amino acid sequences which cause a translated protein to be transported into a membrane and optionally out of the compartment in which said protein was synthesized); thus, the inclusion of identical terms in a Markush-like group renders these terms unclear. The term "fusion protein" is well-known in the art; however, in the instant case, it is unclear whether the extension is a fusion protein itself or if the protein that is the extension is

fused to the portion of the polypeptide that is related to SEQ ID NO:2 to make a "fusion protein". The terms "cleavable peptide" and "uncleaved peptide" are unclear since all peptides are cleavable and since an uncleaved peptide is merely a peptide. The term "Cl-2 like polypeptide" is unclear for the reasons cited below for Cl-2 like and Cl-2 derived.

The addition of residues similar to residues 1 to 18 of SEQ ID NOs: 2 or 12 is confusing because it implies that the additional residues are on the N-terminus; however, no such limitation is expressly stated in the claim.

Appropriate clarification is required for all the above points.

23. Claims 17, 19-25, 28, 32, and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite "**Cl-2 like**" or "**Cl-2 derived**" or "**homologous to Cl-2**", none of which have clear definitions in the art or in the instant specification. The definition for Cl-2 like is found on page 8, lines 16-22, and includes a variety of terms, including "Cl-2 homologs". This definition includes functional OR structural limitations, but does not is not clear as to the metes and bounds of the definition. The definition for Cl-2 derived is found on page 8, lines 13-15, and is less descriptive and more unclear giving no structural and vague functional defining terms. The metes and bounds of the term "homologous" are not defined in the art or the instant specification. Appropriate definitions of the instant terms are required in the claims.

24. Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The particular modification of **A75K or T** is confusing since residue 75 is an asparagine (N) in SEQ ID NO:2.

25. Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The **Markush groups** in Claim 19 and Claim 21 are unclear, particularly in view of the limitation of two or more modifications wherein the limitations are grouped. The Examiner suggests the writing out each possible modification, for example, H18A, H18I, H18L, etc. to ensure that each modification is considered separately to be within the set or two or more.

26. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is similar to the one above for Claim 14. Since the modifications listed are not options in the parent claim, Claim 19, the claim should recite "**further** comprise" (emphasis added) to indicate additional possible modifications. Additionally, the bracketing of the pairs of mutations is confusing (see above).

27. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is similar to the ones above for Claim 14 and Claim 20. The set of modifications that are E23C/R81C and T22C/V82C should be recited as "**comprising**" since these modifications are options in the parent claim. However, V53C/V70C should be recited as

"**further comprising**" since these modifications are not options in the parent claim. Additionally, the bracketing of the pairs of mutations is confusing (see above).

28. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The level to which the insert must be **enriched** with essential amino acids is unclear since "enriched" is a relative term and no sequence is set forth for comparison.

29. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **No SEQ ID NO** is set forth in the instant claim for the corresponding positions cited.

30. Claims 28, 29 and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "**conservatively modified**" and "**conservatively substituted**" are unclear. A definition is set forth in the instant specification on page 9, line 17; however, this definition has little limitation and also has undefined terms, like "chemically similar".

31. Claims 31 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 31, the phrase "**wherein the % sequence**...Weight of 4" is

unclear as to whether or not the entire sequence or only any 23-mer is limited to be within 79% sequence identity.

32. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**immunologically reactive**" is undefined. Appropriate clarification is required.

33. Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "**a** wild-type Cl-2 polypeptide" is confusing since only a single, native, wild-type Cl-2 polypeptide is described in the instant specification, that is SEQ ID NO:2. The article "a" indicates *any*, meaning more than one.

34. Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is similar to the one above for Claims 14, 20, and 24. The **parentheses** around the pairs of mutations is confusing (see above).

35. claims 78-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is confusing how a **23-mer polypeptide** can correspond to **positions 19-83** of another sequence, especially considering the broad sequence identity limitations.

36. Claim 86 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is similar to the one above for Claims 14, 20, 24, and 71. The **parentheses** around the pairs of mutations is confusing (see above).

37. Claim 88 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following **genbank accession numbers**, as found in Claim 88, cannot be defined: A01293, S37493, S33547, A01291, and A39547. The following genbank accession numbers are nucleic acid sequences, not protein sequences as indicated in the claim: Y08625, Z46949, U30861, and AC005770. Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

38. Claims 9-25, 28-31, and 54-89 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to polypeptides having particular structural features, such as percent identity, percent mole

composition, or modifications at particular positions of a defined structure, in the absence of *any* functional features.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant claims are drawn to polypeptides having particular structural features, such as percent identity, percent mole composition, or modifications at particular positions of a defined structure, in the absence of functional features. The instant specification describes these polypeptides in terms of structure **and** function, wherein the function is to act as a nutritional supplement. Thus, Applicants have described the claimed polypeptides in terms of structural and functional features; however, the claims do not recite the described function. Since the function of the claimed invention is extremely broad (any polypeptide can act as a nutritional supplement), the inclusion of such a functional clause in the instant claims will serve to identify

the intended use of the products in the claims, which use is within the description in the instant specification. The intended use is required to define the claimed genus, as described, so that a polypeptide within scope of the structural limitations but having another intended use, such as enzymatic activity, would be considered a non-obvious species of the genus.

The Examiner suggests amending the claims to recite the intended use of the claims polypeptides, that is "wherein the polypeptide is a nutritional supplement".

39. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to any polypeptide that reacts with antibodies to SEQ ID NO:20 and not with antibodies against SEQ ID NO:2.

The Court of Appeals for the Federal Circuit has recently held as described above. The instant claim has no definite structural feature. Moreover, the function of being reactive with antibodies is wholly dependent on said structure. The instant specification fully describes polypeptide fragments of disclosed sequences which can interact with antibodies. However, the instant specification has not described all polypeptide fragments which would interact with the noted antibodies.

40. Claims 87-89 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. The instant claim is drawn to polypeptides which are homologous to Cl-2.

The Court of Appeals for the Federal Circuit has recently held as described above. The instant claims have no defined structural features considering the lack of clarity of the term "homologous". The instant claims also have no defined function.

The Examiner suggests amending the claims to include definite structural characteristics as well as a defined function as noted above.

41. Claims 10-25, 28, 32, 56-58, and 61-89 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for polypeptides having a structure highly related to SEQ ID NO:2 so that corresponding residues can be identified, does not reasonably provide enablement for polypeptides *not* having a structure highly related to SEQ ID NO:2 so that corresponding residues *cannot* be identified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The instant claims are drawn to polypeptides comprising sequences which correspond to SEQ ID NO:2 and are modified at particular corresponding positions. However, the ability to correspond SEQ ID NO:2 with all polypeptide would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Polypeptides require a sufficient amount of relatedness to be aligned; such an alignment is required to identify corresponding positions. A large amount of experimentation would be required to determine corresponding positions in sequences which cannot easily be aligned to SEQ ID NO:2. Applicants present no guidance or working examples of such difficult alignments. In particular, it would be impossible to predict corresponding residues in the absence of sufficient structural relatedness. Thus, one of skill in the art would be required to perform undue experimentation to make the claimed products to the full extent of the claimed scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

42. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Kleber-Janke et al. The instant claims are drawn to polypeptides with at least 30% sequence identity with SEQ ID NO:2 and having 15 mole % lysine.

Kleber-Janke et al. teach a 68 amino acid peptide which is 43% identical to SEQ ID NO:2 (see attached alignment). Said peptide contains 10 lysine residues resulting in a mole percent of 14.7% (rounded up to 15%).

43. Claims 10, 12, 13, 15-18, 28, and 87-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Heim et al. The instant claims are drawn to polypeptides which are versions of SEQ ID NO:2 having seven or more essential amino acid residues at particular positions corresponding to SEQ ID NO:2 where SEQ ID NO:2 does not have essential amino acids. Said polypeptide also has a D74T modification with respect to SEQ ID NO:2. Said polypeptide is also homologous to known CI-2 polypeptides. Due to the confusing language of Claim 10 (see 112, second paragraph rejections above), polypeptides with changes other than at the identified positions meet the limitations of the instant claims.

Heim et al. teach a 212 amino acid protein having the following alterations with respect to SEQ ID NO:2 as aligned: S31T, L40T, Q41L, M59L, Y61L, D74T, I76V, Q78H, and R81H (the underlined modifications meet criteria of Claim 10). While these are not the only changes with respect to SEQ ID NO:2, the scope of the instant claims ("modified to contain") is unclear as noted above. Having a reduced inhibitory activity against various proteases is inherent in the polypeptide of Heim et al. to the extent that the "reduced" activity is defined (see above). The

polypeptide of Heim et al. has ten amino acids prior to the "corresponding" amino acids which can be considered an N-terminal extension which is nutritionally enhancing and which is an uncleaved peptide and which at least one residue of SEQ ID NO:2 residues 1-18. The polypeptide of Heim et al. is homologous to known CI-2 polypeptides to the extent that "homologous" is defined (see above).

44. Claims 19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Cordero et al. The instant claims are drawn to polypeptides having two or more particular modifications corresponding to SEQ ID NO:2.

Cordero et al. teach a 73 amino acid polypeptide with the following modifications with respect to SEQ ID NO:2: Q41K, I49V, and V79T (underlined modifications meet the criteria of Claim 21). While these are not the only changes with respect to SEQ ID NO:2, the scope of the instant claims ("CI-2 derived" and "corresponding to") is unclear as noted above.

45. Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Clausen et al. (WO 92/05239 A, IDS Paper No. 14). The instant claim is drawn to polypeptides related to SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, or 20.

Clausen et al. teach an 83 amino acid polypeptide with high levels of relatendness to the above sequences (see attached alignments). The Examiner notes that the terms "conservatively modified" and "conservatively substituted" are unclear.

Conclusion

46. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy Ponnathapura can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-0000 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPURA ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER

KMK
May 22, 2001